Epidemiology, Containment, and Response to *C. auris* and CP-CRE

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Disclosures

- None

Focus

- Carbapenemase-producing Gram-negative Bacilli

Carbapenem-Resistant Enterobacteriaceae (CRE)

Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA)

Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

The new kid on the block

- *Candida auris*

Why is *Candida auris* a public health threat?

- Highly drug-resistant yeast
- Causes invasive infections associated with high mortality
- Spreads easily in healthcare settings
- Difficult to identify

All the makings of a fungal superbug!

Major Antifungal Resistance Seen

1

>90%

Azoles

2

7%

Echinocandins

3

35%

Polyenes

- **>40% multidrug resistant**
- **A few resistant to all three classes**

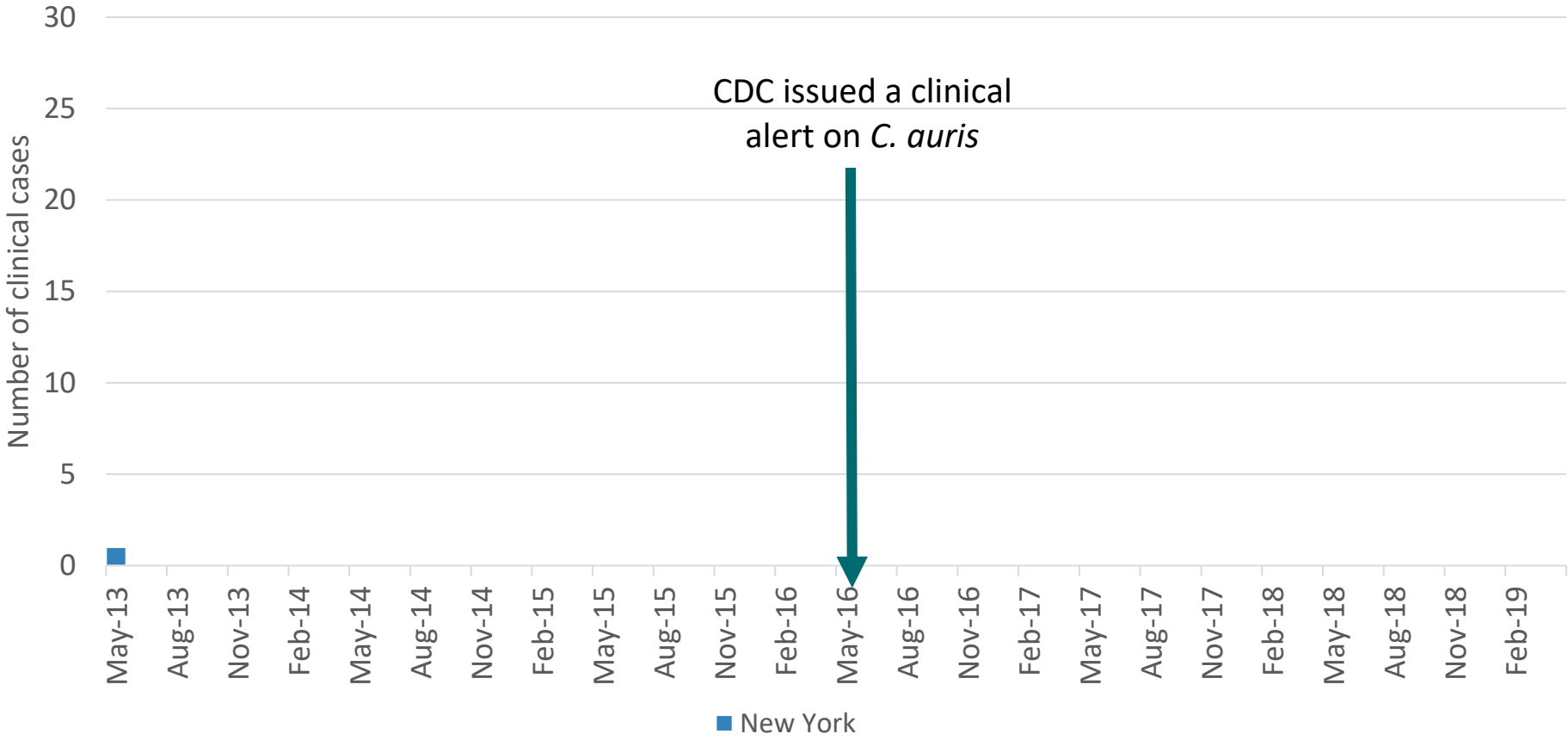
Causes invasive infections

- 50% of clinical cases are bloodstream infections
- 40% in-hospital mortality in BSI cases

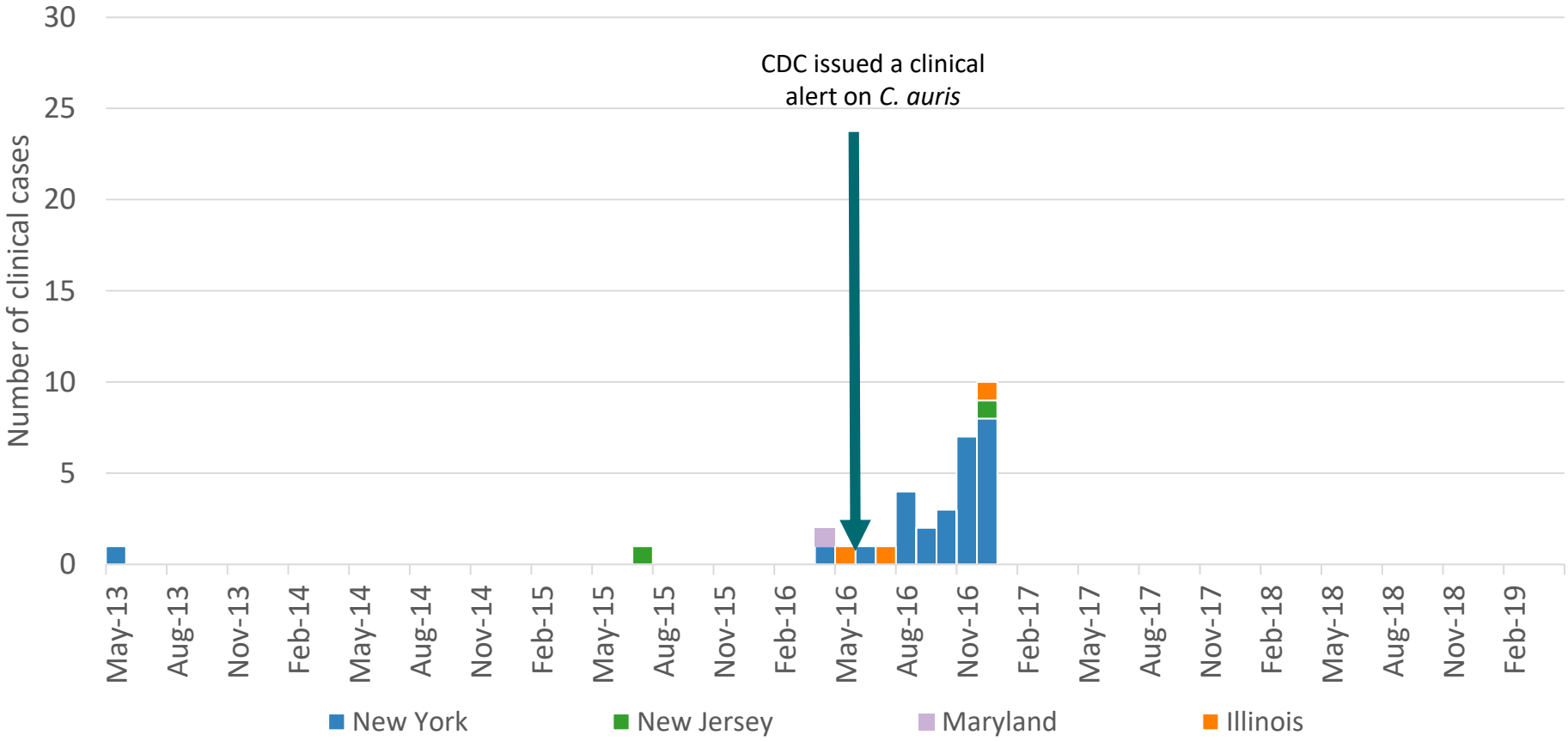
Affects the sickest of the sick

- Older age
- Multiple healthcare stays (acute and long term)
- PEG
- Central catheters
- Tracheostomy
- Ventilator
- On antibiotics and antifungals

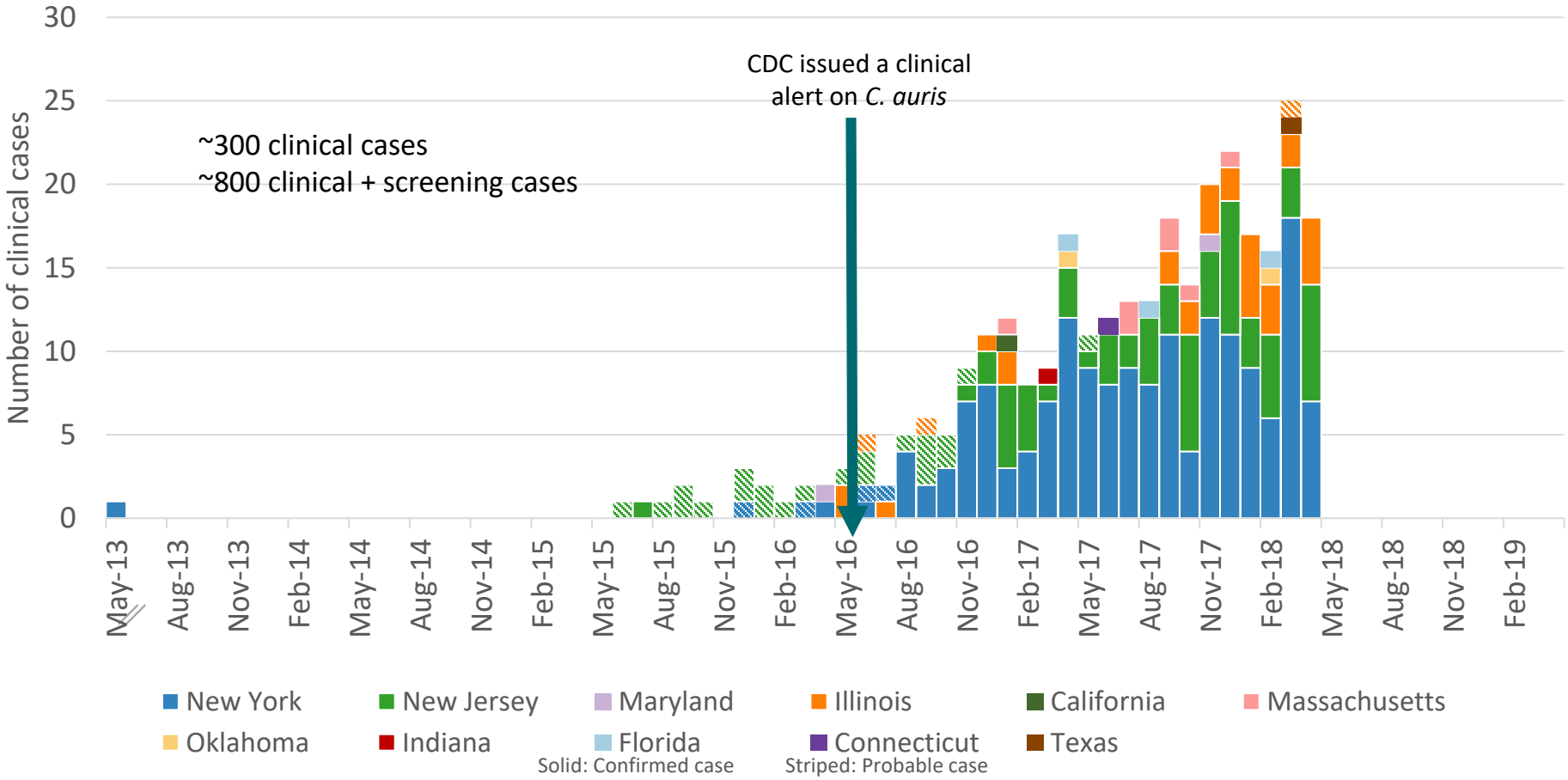
C. auris clinical cases reported by state — United States, June 2016



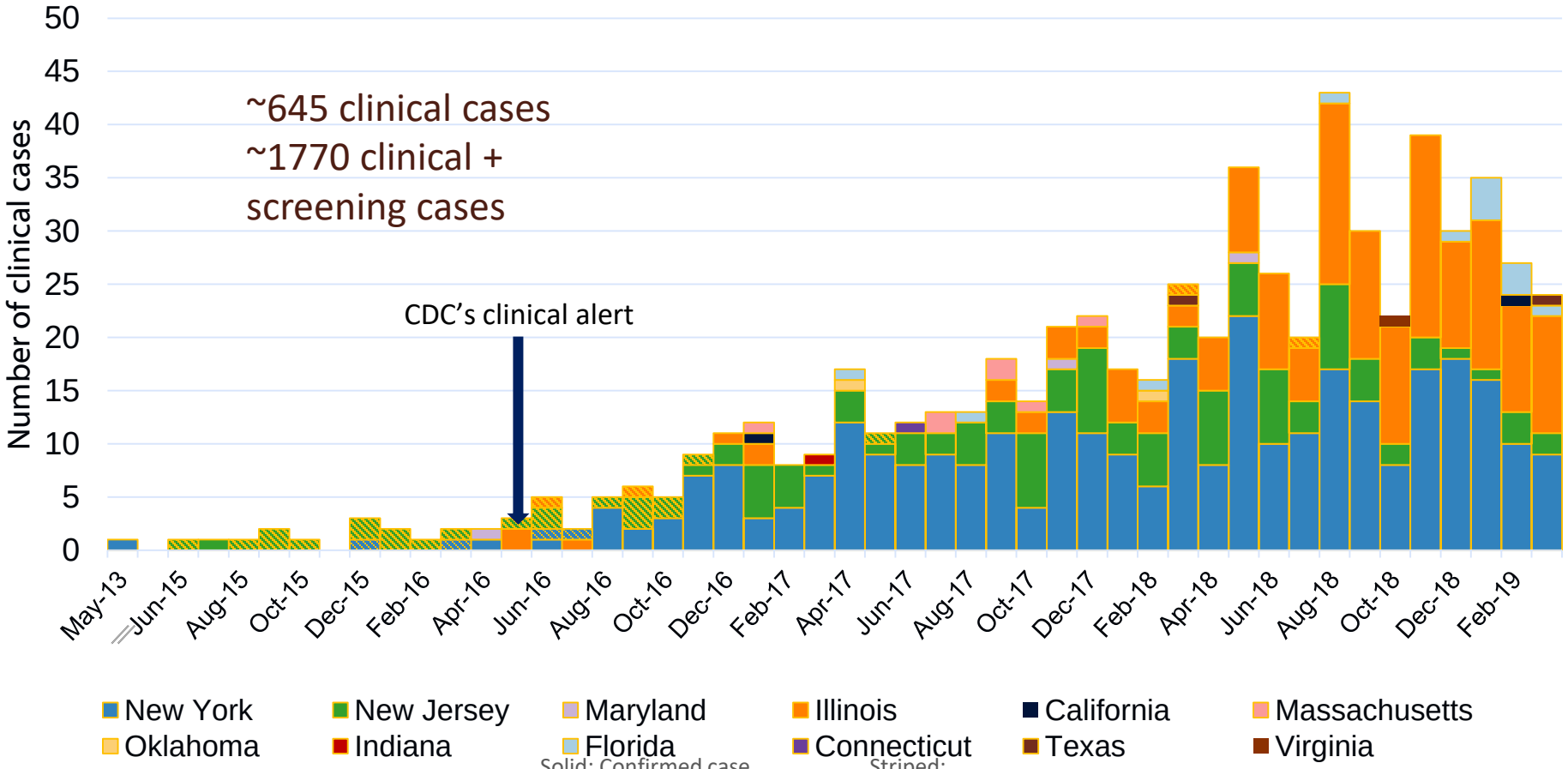
C. auris clinical cases reported by state — United States, 2013–December 2016



C. auris clinical cases reported by state — United States, 2013–April 2018



C. auris clinical cases reported by state — United States, 2013–March 2019



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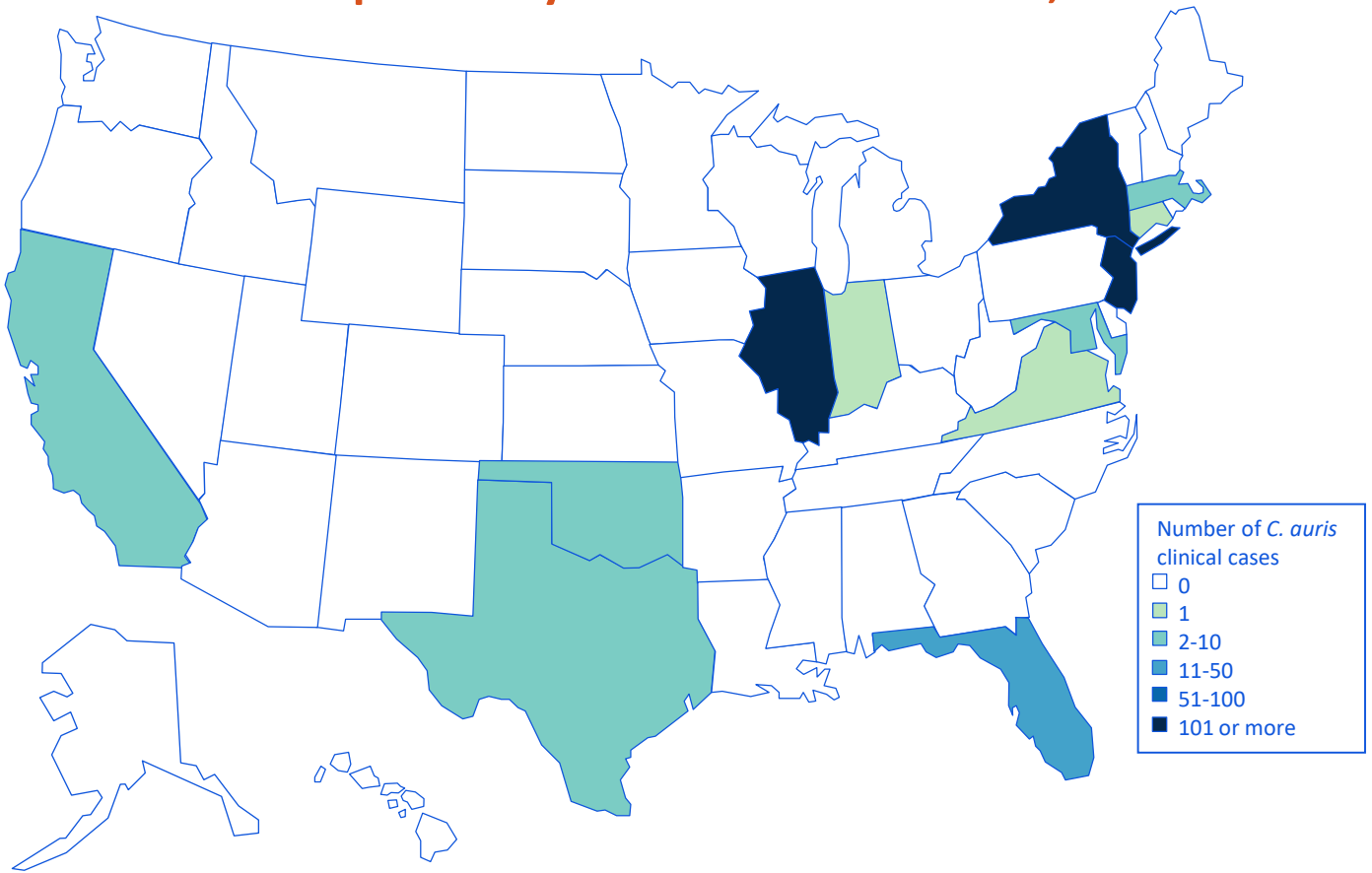
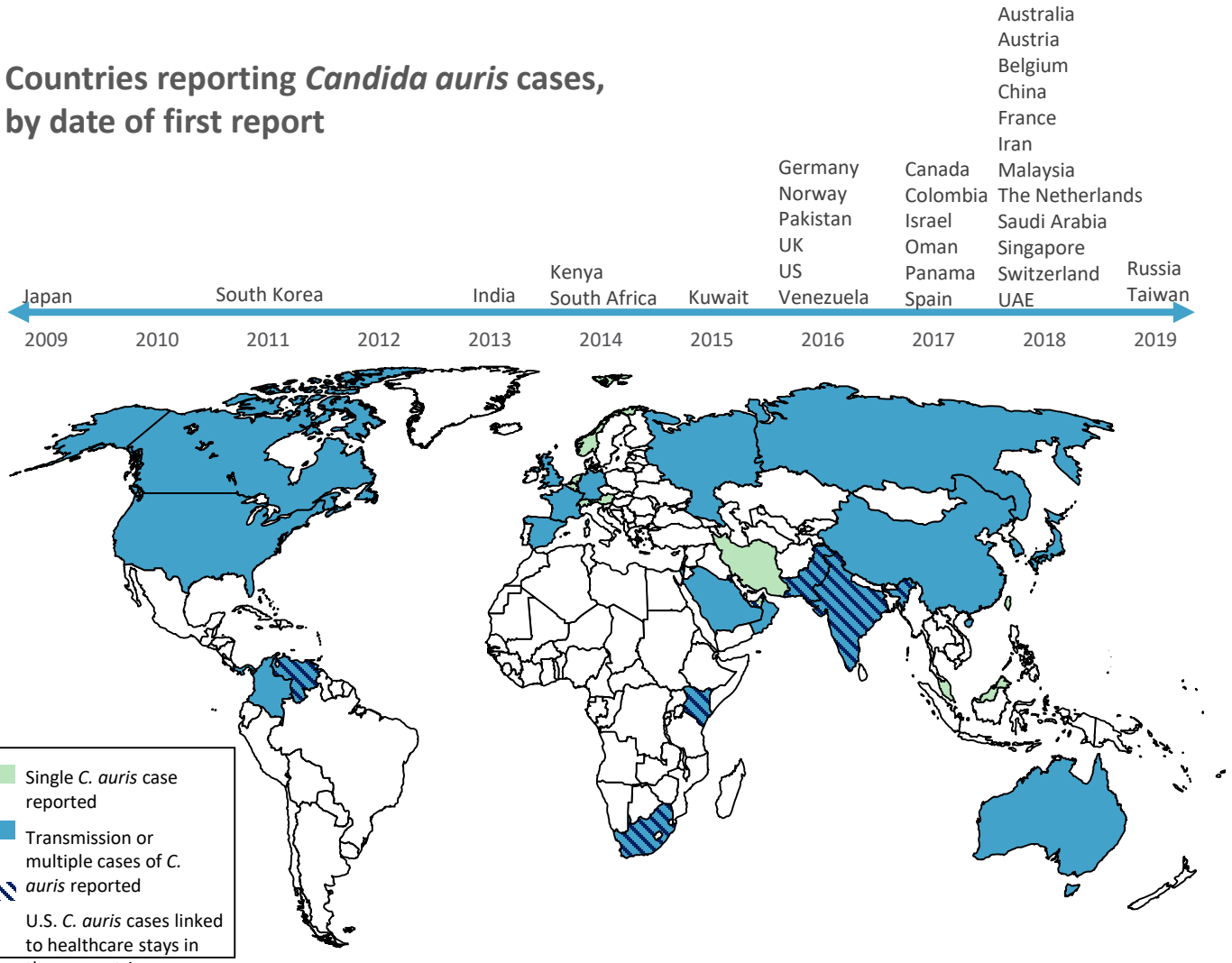


Countries reporting *Candida auris* cases, by date of first report



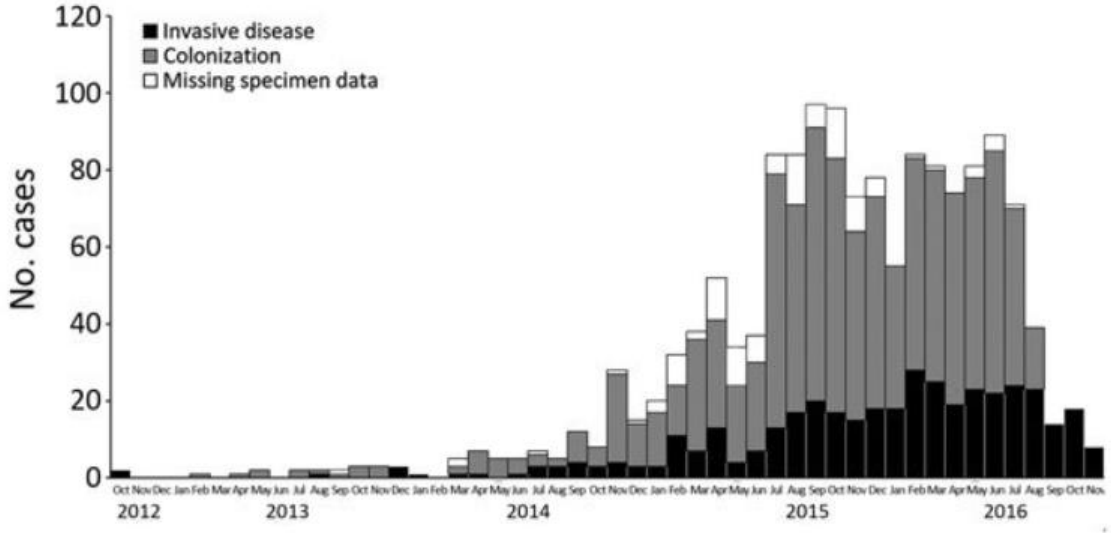
India

- 2011-2012 Study of 27 ICUs in India
  - 19 already had *C. auris*
  - 5% of candidemia in ICUs was *C. auris*
  - As high as 50% in some hospitals

Rudramurthy et al, *Candida auris* candidaemia in Indian ICUs: analysis of risk factors, JAC 2017

South Africa

- 10% of Candidemia in multisite surveillance in South Africa was due to *C.*

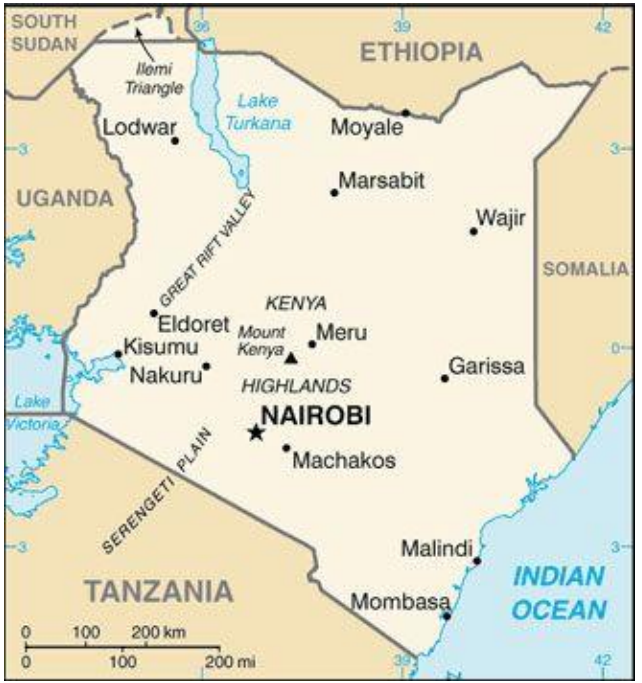


Distribution of cases of *Candida auris* by type of infection and date of specimen collection, South Africa, 2012–2016. n = 1,306.

Govender et al, *Candida auris* in South Africa, 2012–2016 EID 2018

Kenya

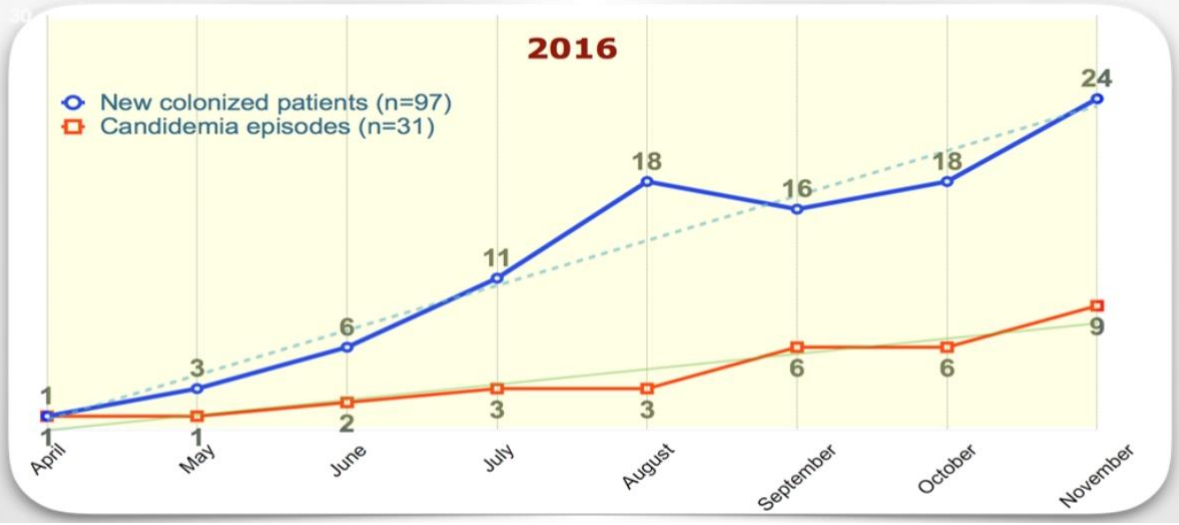
- 2010 → 2016 in a leading hospital in Kenya
  - 38% *C. auris*
  - 25% *C. albicans*
- Candidemia was the leading cause of BSIs in their ICU



R. Adam et al. *Candida auris* fungemia: Risk factors and outcome; IDWeek 2018

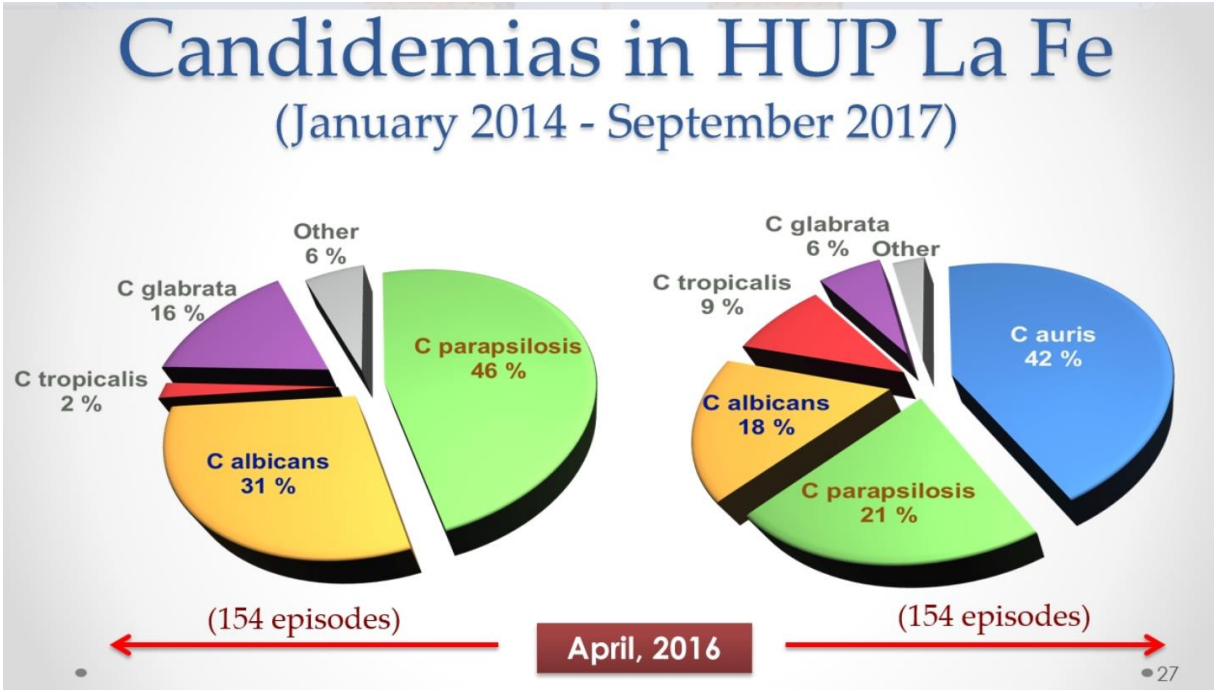
Spain

- The **peak** incidence occurred in **November 2016**:
  - **9 candidemia** episodes (SICU and ICU patients)
  - **24 new colonized** patients



Ruiz-gaitan et al, Mycoses, 2018

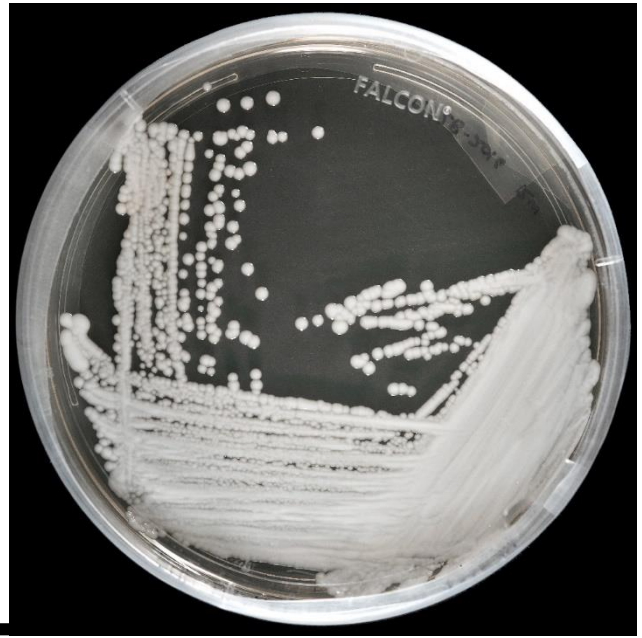
Spain

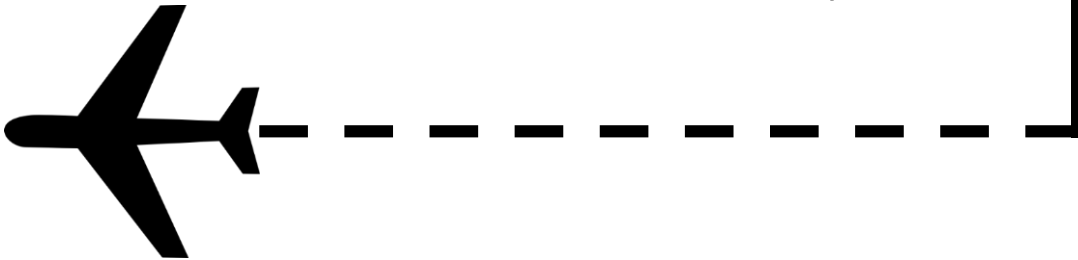


https://www.eccmidlive.org/#resources/how-should-we-manage-the-c-auris-outbreak

Twelve cases linked to healthcare abroad

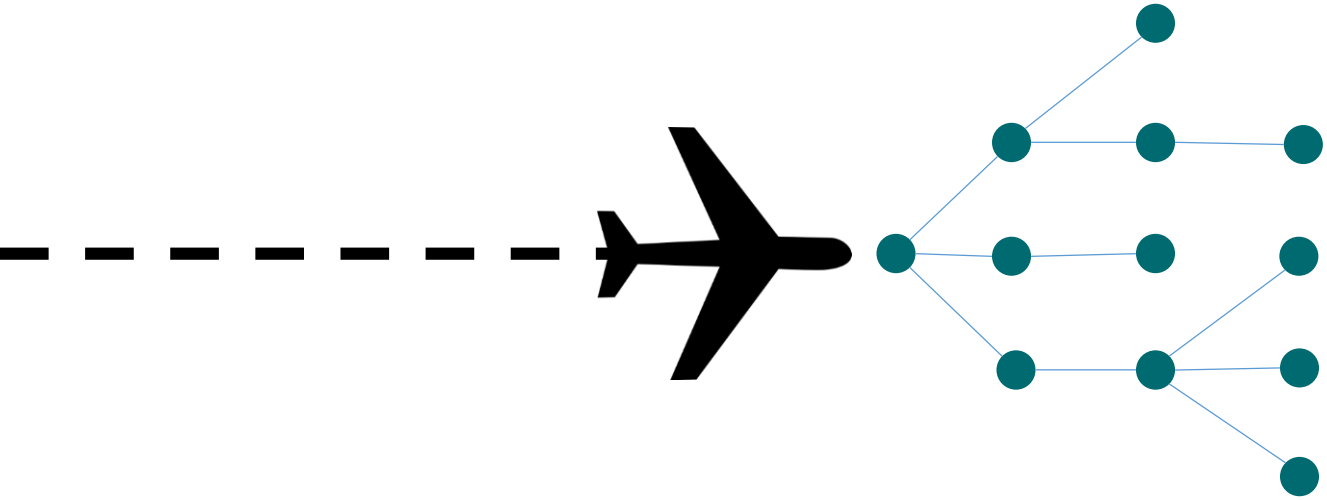
- Patients from India, Pakistan, South Africa, Kenya, and Venezuela
- Identified weeks to two years after hospitalization in that country
- WGS showed isolates were related to those from the countries where patients received healthcare
- Isolates were from all different body sites



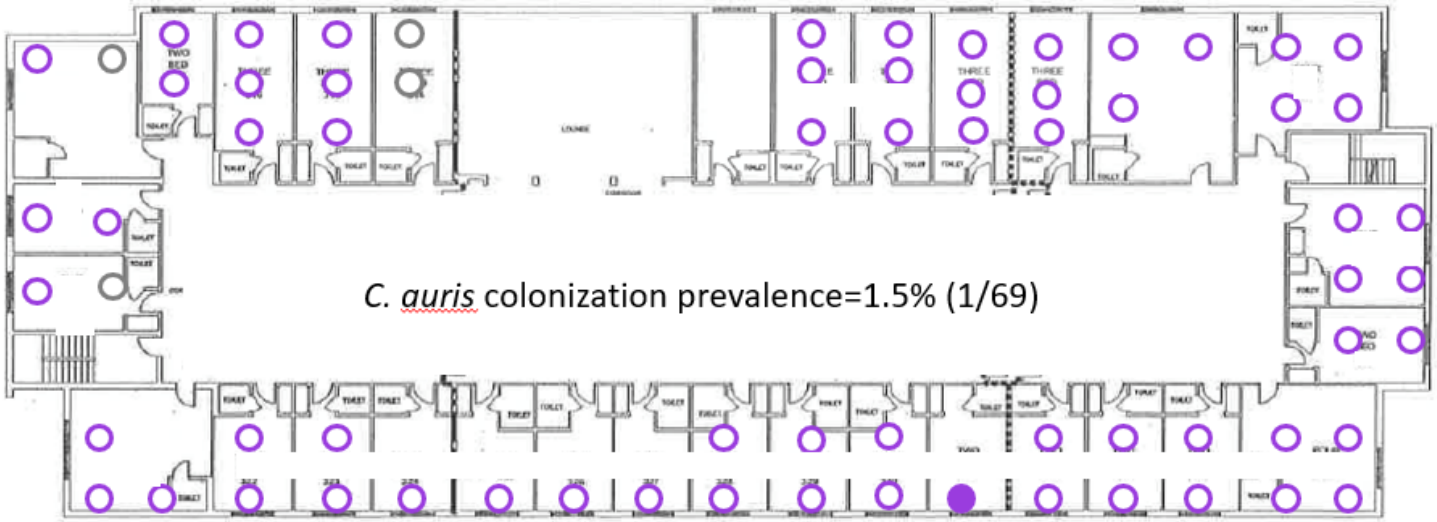


Healthcare abroad is risk factor for *C. auris*

- Majority of US cases don’t have links to healthcare abroad
- US *C. auris* cases are a result of introductions from abroad followed by local transmission



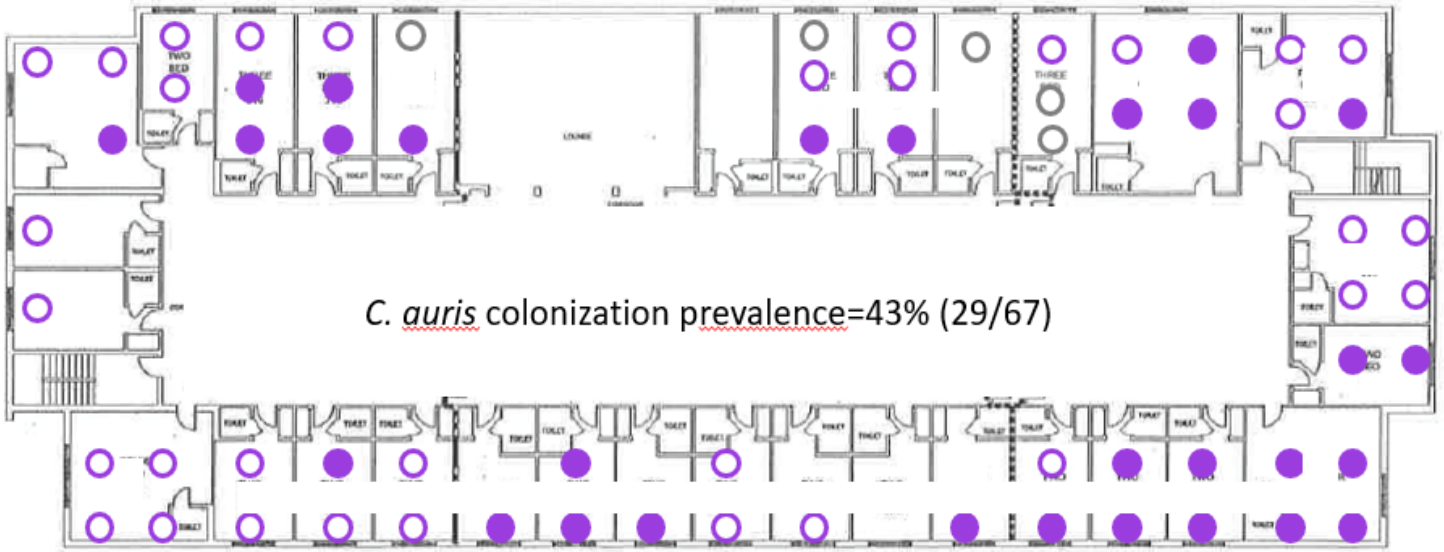
vSNF A Ventilator/Trach Floor
March 2017 *C. auris* PPS Results



- *C. auris* positive
- Screened negative for *C. auris*
- Not tested for C. auris (refused or not in room)

Slide courtesy of Chicago Department of Public Health.

vSNF A Ventilator/Trach Floor
January 2018 *C. auris* PPS Results



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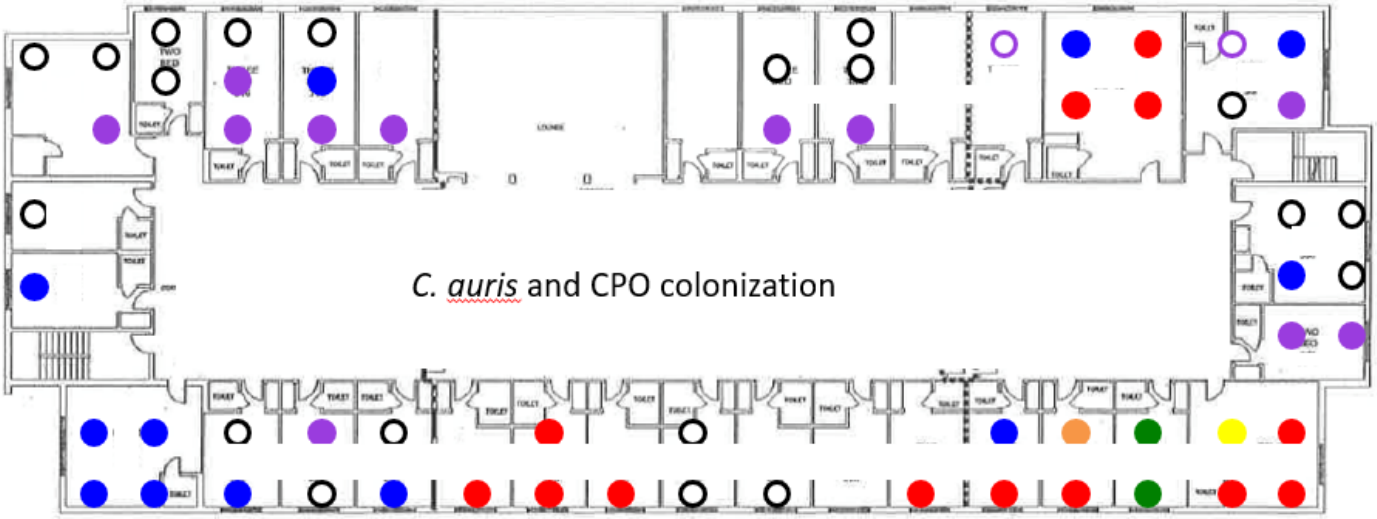
Slide courtesy of Chicago Department of Public Health.

vSNF A Ventilator/Trach Floor
January 2018 CPO and *C. auris* PPS Results



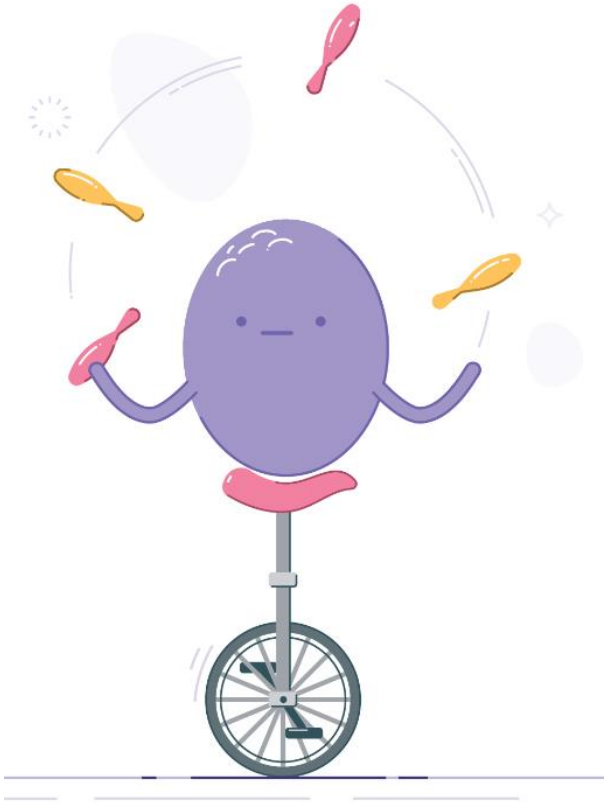
- *C. auris*
- *C. auris* and KPC
- KPC or CRE with unknown mechanism of resistance
- *C . auris*, KPC, and NDM
- *C. auris*, VIM-CRPA, and KPC
- *C. auris* and KPC-CRPA

- Screened negative for *C. auris*, but not tested for CRE
- Screened negative for CRE and *C. auris*

Slide courtesy of Chicago Department of Public Health.

It’s new bug using old tricks

- Drug resistant, makes people sick, and spreads
- Similar to CRE, VRE, MRSA, and other drug resistant bugs
- We are still learning a lot about *C. auris*, but we also know how to control the spread of other similar germs
  - Many of the same principles can be applied to *C. auris*



C. auris has uncovered some weaknesses

- Laboratory capacity
- Infection control
  - Environmental disinfection
- Nursing home infection control practices
- Inter facility communication on transfer

What can you all do in Michigan?

- Early detection of *C. auris*
  - Find out if your lab has capacity to detect *C. auris*
  - Make sure all invasive isolates of *Candida* are determined to species level
  - Determine species of *Candida* in non-sterile sites if patient has hospitalization abroad or is in or coming from an LTACH or vSNF
  - Consider screening patients with overnight hospitalization abroad, especially with they also have a CPO.
- Bolster infection control practices pre-emptively
  - Audit hand hygiene
  - Medical equipment disinfection practices
  - Environmental disinfection

CPOs

Carbapenem Resistant Gram Negative Bacilli

	Percent Carbapenem Resistant[1,2]	Incidence of Carbapenem Resistant Isolates per 100,000 persons
Enterobacteriaceae		7.48[3]
Klebsiella spp.	6.9	
Enterobacter spp.	6.2	
E. coli	0.7	
A. baumannii	43.2	0.76[4]
P. aeruginosa	20.7	14.5[4]

[1]Adult Device-associated Infections in ACHs reported to National Healthcare Safety Network Device and Procedure Module, 2015-2017
[2]Percent carbapenem-nonsuceptibile shown for CRPA and CRAB
[3]Duffy et. Al., Effect of Carbapenem-Resistant Enterobacteriaceae (CRE) Surveillance Case Definition Change on CRE Epidemiology - Selected U.S. Sites, 2015-2016, IDWeek 2018.
[4]Emerging Infections Program Healthcare-Associated Infections-Community Interface (HAIC)

Data preliminary; subject to change

Carbapenemases

- **Enzymes that degrade carbapenems**
- **Encoded on mobile genetic elements**
- **Can rapidly increase percent carbapenem resistant**

KPC - *Klebsiella pneumoniae* carbapenemase
OXA-48 – Oxacillinase-48-type carbapenemase
NDM – New Delhi Metallo-β-lactamase
VIM – Verona Integron-encoded Metallo- β -lactamase
IMP – Imipenemase Metallo- β –lactamase

β-lactam/β-lactamase inhibitor combinations

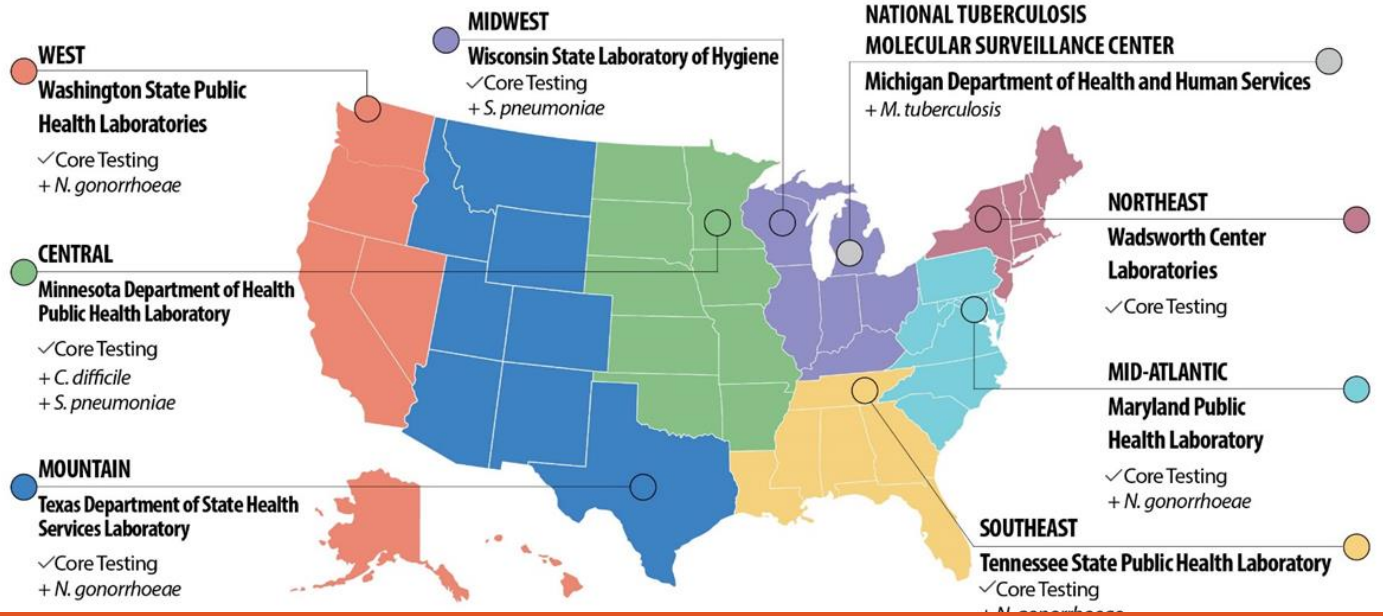
OXA-23, OXA-24/40, OXA-58, OXA-235 –
Oxacillinases with carbapenemase activity
-most frequently identified in *Acinetobacter* spp.

Limited Ability to Detect Carbapenemases at Clinical Laboratories

- Among 4,685 acute care hospitals completing NHSN Facility Survey in 2016
  - 50% served by lab that performed carbapenemase testing for CRE
    - 80% used phenotypic testing methods
    - 18% used molecular methods

Shugart A, et al. (2018). Hospital microbiology laboratory practices for Enterobacteriaceae: Centers for Disease Control and Prevention National Healthcare Safety Network (NHSN) annual survey, 2015 and 2016. Infection Control & Hospital Epidemiology 2018, 39, 1115–1117. doi: 10.1017/ice.2018.153

Antibiotic Resistance Laboratory Network



Carbapenemase testing for CRE and CRPA at 56 state and local public health laboratories.
Sentinel surveillance for carbapenemases in *Acinetobacter baumannii.*
Colonization screening for carbapenemases
Confirmatory testing and colonization screening for *Candida auris.*

CRE Update

CP-CRE by Mechanism, AR Lab Network, January 2017 – December 2018

	CRE N=21,422 No. (%)#
Carbapenemase producing*	8145
KPC	7076 (87)
NDM	562 (7)
OXA-48-type	299 (4)
VIM	62 (1)
IMP	76 (1)

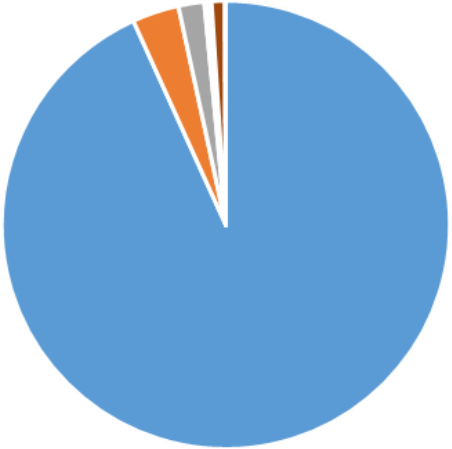
*Carbapenemase-producing defined as positive by phenotypic carbapenemase activity test or by molecular assay for one of 5 carbapenemases

#105 CP-CRE and 3 CP-CRPA had >1 carbapenemase identified

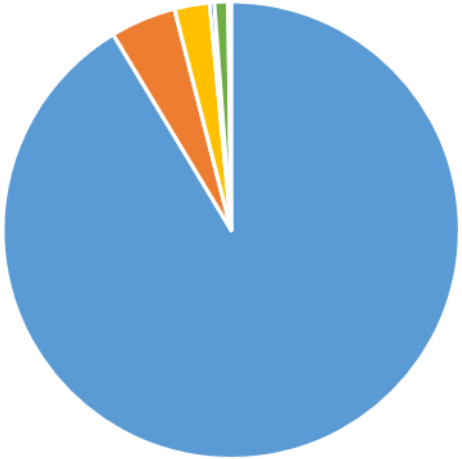
Preliminary data; subject to change

Carbapenemases Identified in *Klebsiella*, *Enterobacter*, and *E. coli*

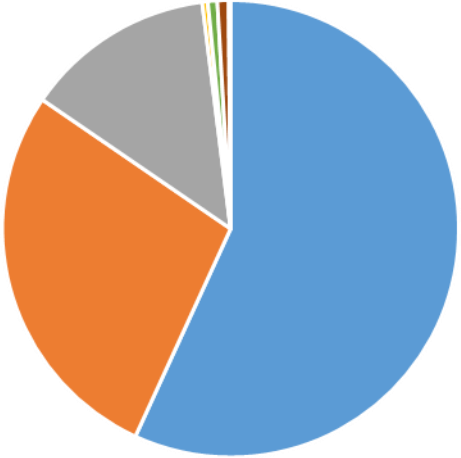
Klebsiella spp.



Enterobacter spp.

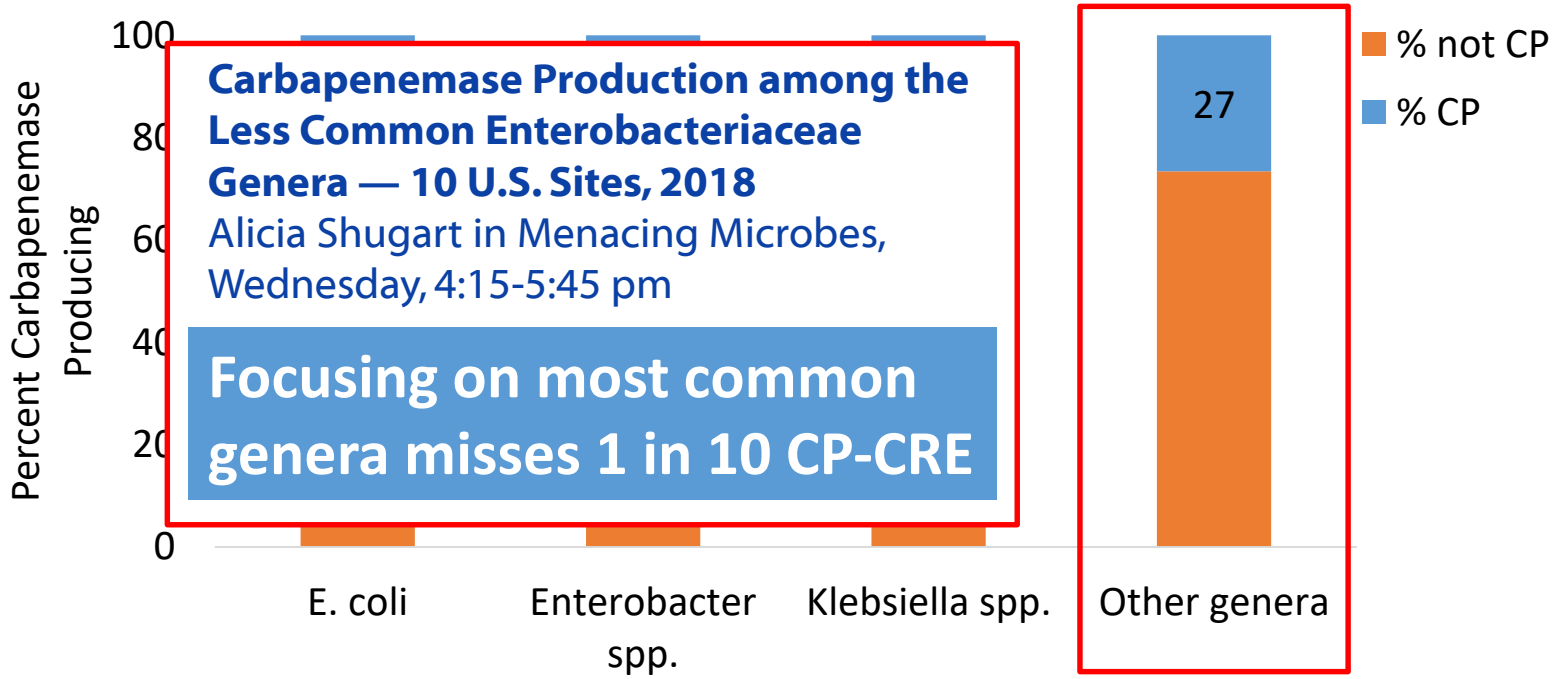


E. coli



KPC+ NDM+ OXA+ VIM+ IMP+ NDM+KPC+ VIM+KPC+ NDM+OXA+ OXA+KPC+

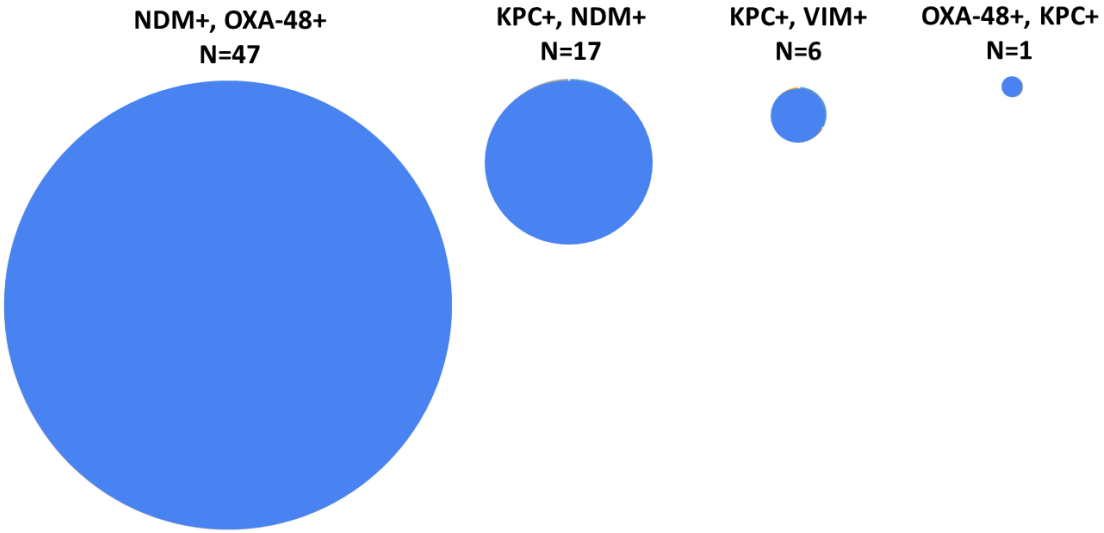
Percent of CRE that are Carbapenemase Producing (CP), by Genera (N=8,145), AR Lab Network 2017–2018



CP-CRE is positive for mCIM or Carba-NP or PCR positive for one carbapenemase genes.
For Enterobacter, CP-CRE is defined as positive for at least one carbapenemase genes.

CRE with Multiple Carbapenemases, by Organism and Mechanism, N=71*

- Reports of CRE with >1 carbapenemase from October 2012 to November 2018
- Limited analysis to patient's first isolate for organism-mechanism combination
  - Identified 71 isolates from 67 patients



Cal Ham, CDC

Data are Preliminary and Subject to Change

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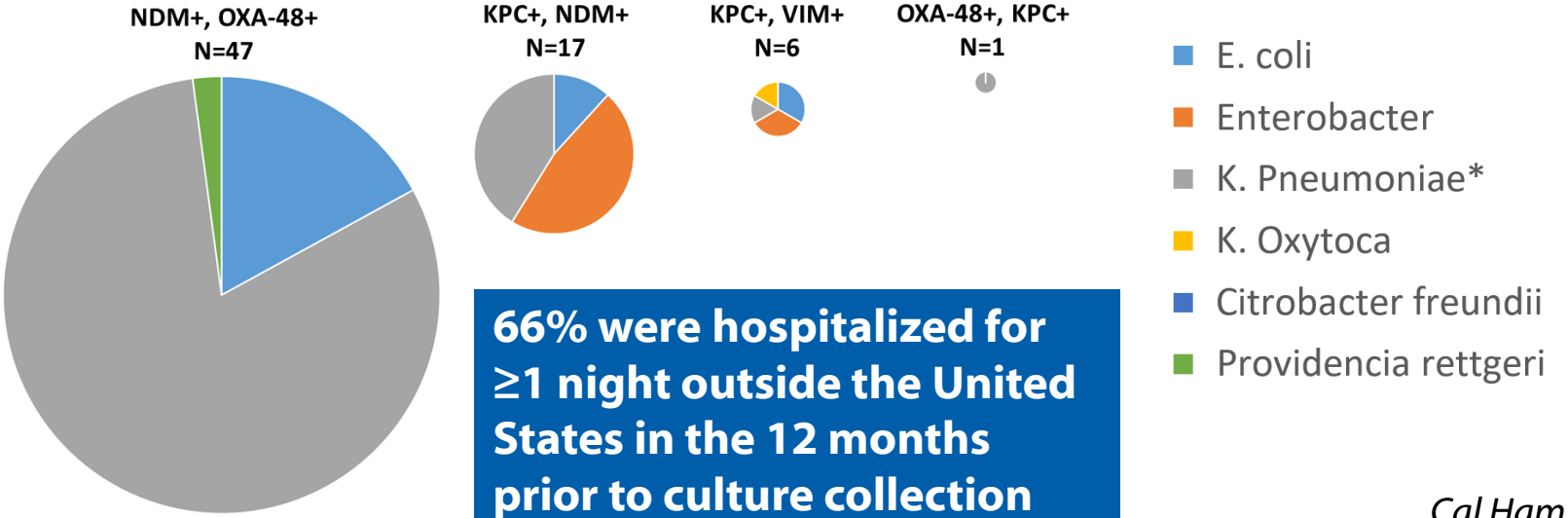


66% were hospitalized for ≥1 night outside the United States in the 12 months prior to culture collection

Cal Ham, CDC

Data are Preliminary and Subject to Change

CRPA Update

CRPA by Mechanism, AR Lab Network, January 2017 – December 2018

	CRPA N=14,141 No. (%)
Carbapenemase producing*	458 (3)
KPC	85 (19)
NDM	17 (4)
OXA-48-type	0
VIM	186 (41)
IMP	16 (3)

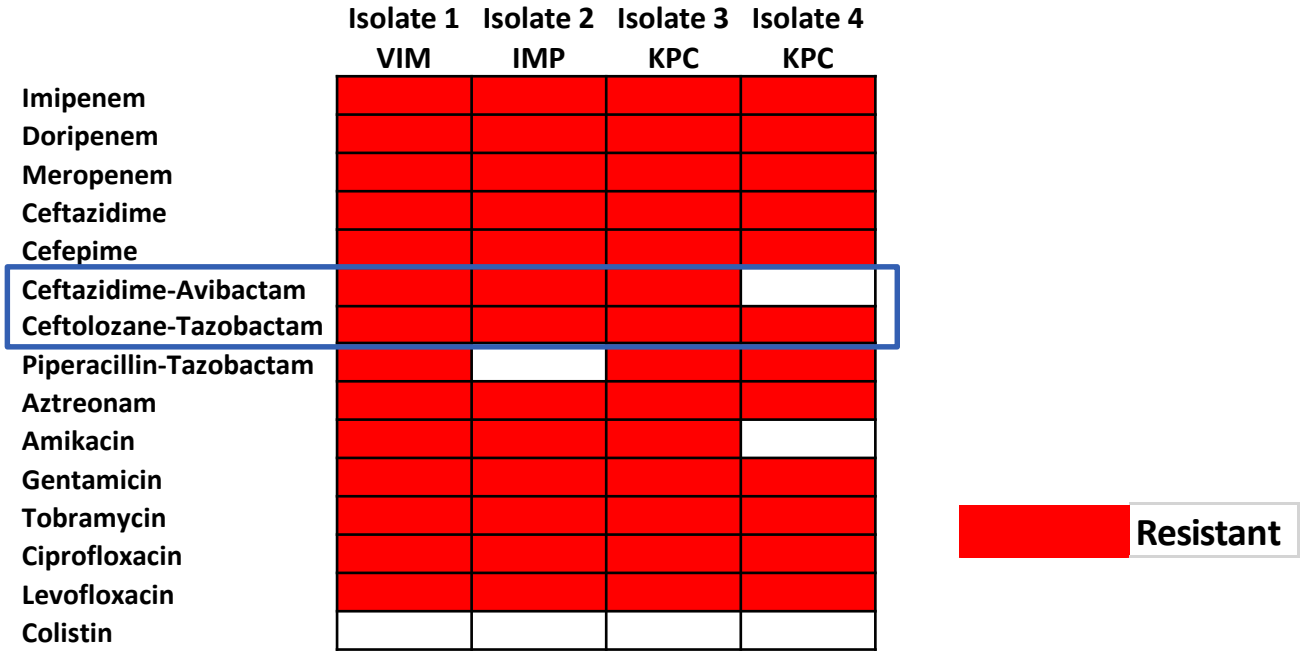
*Carbapenemase-producing defined as positive by phenotypic carbapenemase activity test or by molecular assay for one of 5 carbapenemases

3 CP-CRPA had >1 carbapenemase identified

Preliminary data; subject to change

Carbapenemase-Producing *P. aeruginosa* Are Highly Resistant

Broth microdilution antimicrobial susceptibility, CP-CRPA Isolates from 4 Patients Identified through EIP CRPA Surveillance, 2016-2018



Preliminary data; subject to change

CRAB Update

Carbapenemases in *Acinetobacter*

- Can acquire carbapenemases including OXA variants typically only associated with *Acinetobacter*
  - E.g. 23, 235 (237), 24/40 (72), 58
- Other OXA variants are intrinsic to *Acinetobacter*
  - E.g. 51
- Acquired Carbapenesases also found in Enterbacteriaceae
  - E.g. KPC and NDM
- Concern for accelerated spread in high risk clones (e.g. ST 2)
  - Associated with outbreaks in other countries

Absence of Promising New Therapies for Carbapenem-resistant *Acinetobacter baumannii*

WHO priority pathogens list for R&D of new antibiotics

Priority 1: CRITICAL

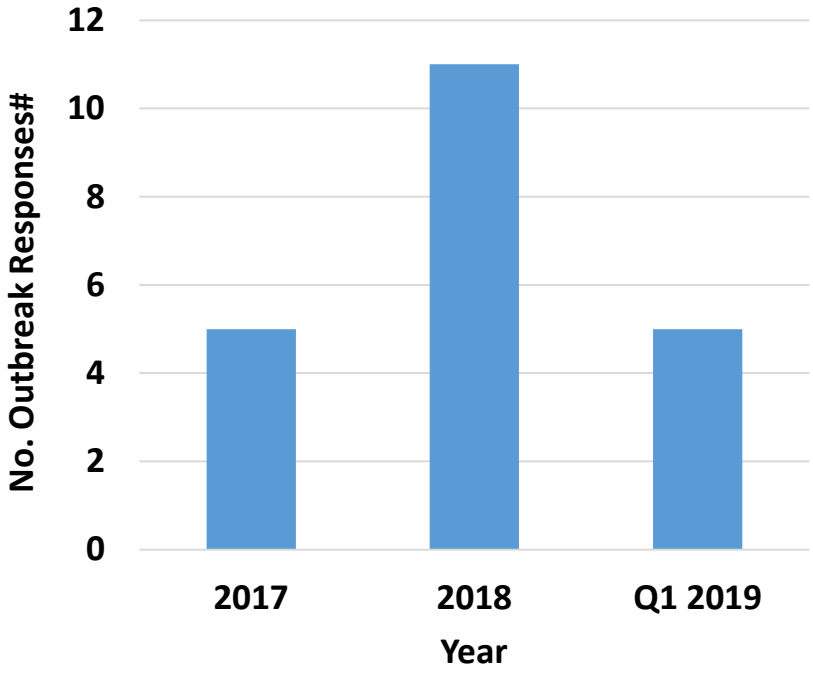
- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Anticipated Activity of New Antibiotics

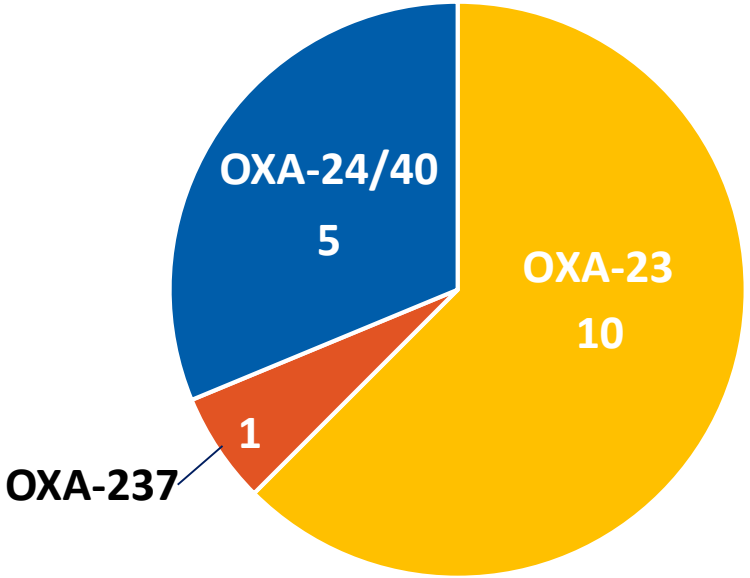
Drug	CRE	CRPA	CRAB	Stage
Ceftazidime-avibactam	✓	X	X	FDA Approved
Meropenem-vaborbactam	✓	X	X	FDA Approved
Plazomycin	✓	X	X	Submitted to FDA
Imipenem-relebactam	✓	✓	X	Phase 3
Eravacycline	✓	✓	X	Phase 3
Cefiderocol	✓	✓	✓	Phase 3
Omadacycline	X	✓	X	Phase 3
LYS228	✓	X	X	Phase 2
Murepavadin	X	✓	X	Phase 2
Cefepime-AAI101	✓	X	X	Phase 2

https://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

Increase in CRAB Outbreaks Reported to CDC



All CRAB Outbreaks Reported During 2018-2019 had Carbapenemases Associated, N=16



#Outbreak defined as ≥2 epidemiologically linked cases
Data are preliminary and subject to change.

CP-*A. baumannii* Outbreaks, 2018-2019

- Acute care hospitals (MICU, NICU, Burn units), LTACHs, high acuity SNFs
  - Often involve multiple units and facilities
- Linked to environmental contamination: portable chest x-ray, wound care scissors, patient chair, sink basin, keyboards, Pyxis
- Isolates often highly resistant

Example Susceptibility of OXA-23-producing CRAB

BMD Tests	RESULT	INTERPRETATION
Amikacin	64 µg/mL	Resistant
Ampicillin-sulbactam	16/8 µg/mL	Intermediate
Cefepime	>32 µg/mL	Resistant
Cefotaxime	>64 µg/mL	Resistant
Ceftazidime	32 µg/mL	Resistant
Ceftriaxone	>32 µg/mL	Resistant
Ciprofloxacin	>8 µg/mL	Resistant
Colistin	2 µg/mL	Susceptible
Doripenem	>8 µg/mL	Resistant
Gentamicin	>16 µg/mL	Resistant
Imipenem	32 µg/mL	Resistant
Levofloxacin	>8 µg/mL	Resistant
Meropenem	>8 µg/mL	Resistant
Minocycline	<=4 µg/mL	Susceptible
Piperacillin-tazobactam	>128/4 µg/mL	Resistant
Tetracycline	32 µg/mL	Resistant
Tigecycline	2 µg/mL	
Tobramycin	>16 µg/mL	Resistant
Trimethoprim-sulfamethoxazole	>8/152 µg/mL	Resistant

Summary

- Since 2017, the AR Laboratory Network tested >25,000 CRE and CRPA isolates
  - Action to prevent spread of carbapenemase-producing organisms
  - New insights into epidemiology
- Carbapenemase-producing *P. aeruginosa* and *A. baumannii* characterized by large outbreaks, unique challenges for carbapenemase detection
  - CRPA: Incidence high, but carbapenemases rare
  - CRAB: Incidence low, OXA carbapenemases common but limited testing

Action Steps

1. Optimize carbapenemase testing
   - Consider expanding carbapenemase testing to less common genera
   - Test CRE and CRPA isolates for all 5 common carbapenemases
2. Be on high alert for carbapenemases in CRPA and CRAB
   - Monitor clinical cultures and investigate highly resistant isolates, including performing mechanism testing
3. Prevent introductions of novel resistance
   - On admission, screen patients hospitalized outside the U.S. in the prior 6 months for carbapenemase-producing organisms and *C.*

Talk to your state health department about testing available through the AR Laboratory Network

Containment strategy

- Goal: slow spread of novel or rare MDROs or mechanisms
- Systematic, aggressive response to **single cases** of high concern antimicrobial resistance
- Response Tiers
  - Tier 1: Novel resistance mechanisms, PanR
  - Tier 2: Mechanisms and organisms not regularly found in a region
  - Tier 3: Mechanisms and organisms regularly found in a region but not endemic

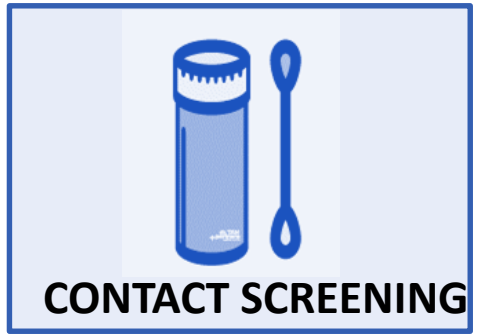
https://www.cdc.gov/hai/outbreaks/mdro/index.html

Containment Strategy

Systematic public health response to slow the spread of emerging AR

Single case of emerging resistance (e.g., pan-R, carbapenemase or MCR-producing Gram negatives)

Onsite assessment using standardized tools



Available through ARLN

Regular infection control assessments and point prevalence surveys until transmission stops

Resources:

- CRE Toolkit
  - https://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html
- Interim Containment Guidance for Novel or Targeted MDROs
  - https://www.cdc.gov/hai/outbreaks/mdro/index.html
- Hand Hygiene
  - https://www.cdc.gov/infectioncontrol/guidelines/hand-hygiene/index.html
- Environmental Cleaning and Disinfection
  - https://www.cdc.gov/infectioncontrol/guidelines/environmental/index.html
- Risk Assessment with Appropriate use of PPE
  - https://www.cdc.gov/hai/prevent/ppe.html
- Guideline for Isolation Precautions
  - https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html
- Reprocessing of Reusable Medical Equipment
  - (https://www.cdc.gov/hicpac/recommendations/flexibleendoscope-reprocessing.html)